Guidance for Industry

Efficacy Evaluation of Hemoglobin- and Perfluorocarbon-Based Oxygen Carriers

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

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Comments and suggestions regarding this draft document should be submitted by December 18, 1997, to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number 90N-0349. For questions regarding this draft document, contact Astrid Szeto (CBER), 301-594-3074.

U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY[1]: EFFICACY EVALUATION OF HEMOGLOBIN- AND PERFLUOROCARBON-BASED OXYGEN CARRIERS

I. INTRODUCTION

The material to be presented here will serve as an adjunct to the previously issued (27 August 1990) Points to Consider in Safety Evaluation of Hemoglobin-Based Oxygen Carriers (Transfusion 31: 369-71, 1991) and is intended to serve as additional guidance in design of activity and safety (phase II) studies. This guidance was developed, in part , from presentations and discussions at the Workshop on Criteria for Efficacy of Red Cell Substitutes, held in Bethesda, Maryland on 11 January 1994. The workshop was sponsored by the National Heart, Lung and Blood Institute, the Department of the Army and the Food and Drug Administration (FDA).

While the emphasis in this document will be on appropriate criteria to be used for determination of efficacy of oxygen carriers, issues of safety and efficacy cannot be completely separated from each other and some potential safety concerns will also be addressed. In preparing this document, FDA considered the presentations and discussions at the Workshop on Criteria for Efficacy of Red Cell Substitutes.

"Hemoglobin-based oxygen carriers" refers to products, manufactured from hemoglobin, that could be used as adjuncts or alternatives to the transfusion of red cells. The broader term "oxygen carrier" is used in this guidance since some proposed indications of products involve conditions in which red blood cells are not used.

For the most part, the material presented here will provide general guidance and does not contain specific information for various indications, nor does it provide specific trial designs. Since the range of possible uses for oxygen carriers has not been defined, flexibility is important to avoid the unwanted effect of stifling further development. This guidance is not intended to discourage innovation by

[1] This draft guidance document represents the FDA's current thinking on efficacy evaluation of hemoglobin- and perfluorocarbon-based oxygen carriers. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both. For additional copies of this guidance, contact: (1) the Office of Communication, Training and Manufacturers Assistance, HFM-40, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, or (2) the Drug Information Branch, Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the World Wide Web (WWW) by connecting to: (1) CBER at "http//www.fda.gov/cber/publication.htm", or (2) CDER Home Page at "http://www.fda.gov/cder/guidance/".

manufacturers in the design of clinical trials or in the development of appropriate endpoints and criteria of efficacy.

II. GENERAL COMMENTS

A clinical trial endpoint is the outcome measure used in evaluating a drug's efficacy. Endpoints may be direct measures of clinical benefit (improved survival, alleviation of symptoms) or they may be laboratory measurements or physical signs expected to correlate meaningfully with clinical benefit. The latter are referred to as *surrogate endpoints* and, once validated, are especially important in the case of oxygen carriers since direct demonstration of efficacy is likely to be difficult (as it has been for red blood cells, per se). Validation of a surrogate endpoint for a therapy includes generation of clinical data demonstrating that effects of the therapy on the surrogate endpoint reliably predict effects on a clinical endpoint. Factors of importance when considering acceptability of surrogate endpoints include feasibility of using direct clinical measurements, risk/benefit assessments and, perhaps most importantly, knowledge and understanding of the disease and of the agent.

There has been extensive clinical experience with red cell transfusion, resulting in a practical appreciation of the indications, benefits and risks. There is also an extensive collection of data on red blood cells, the anemic state and their interaction, resulting from years of basic and applied research. Thus, although it is not possible to document the clinical benefit of all red cell transfusions with specific endpoints, the available knowledge relevant to such transfusions supports use of surrogate endpoints, such as the P50, the oxygen content and the hematocrit as suitable endpoints to demonstrate efficacy of red cell transfusions in clinical practice and in some clinical trials. Currently, FDA does not consider these surrogate endpoints to be acceptable as measures of efficacy in trials of red cell substitutes, since knowledge of the effects of hemoglobin-and perfluorocarbon-based red cell substitutes and of the interaction of these agents with various clinical states is rudimentary. Further, no oxygen carrier presently available has all the properties of the human red cell, nor are any two products identical. The endpoints used in clinical studies of these agents should be selected with such caveats in mind.

III. SPECIFIC RECOMMENDATIONS

FDA will consider indications for use of oxygen carriers in three general categories: 1) regional perfusion, 2) acute hemorrhagic shock, and 3) perisurgical applications. These categories have been chosen to simplify the approach to selection of endpoints, but do not represent the only approach, nor are investigators required to accept these categories. The approach will, however, permit us to make some illustrative points:

A. Local Effects/Regional Perfusion

This category might best be defined by considering two examples: perfusion during coronary angioplasty and enhancement of tumor radiosensitivity. Perfusion, via the central lumen of a catheter used for percutaneous transcoronary angioplasty (PTCA), is an FDA-approved indication for a perfluorocarbon preparation (Fluosol™). The data that supported this approval

included clinical studies utilizing surrogate endpoints of left ventricular function which had been validated as clinically relevant by recognized cardiologic investigations. Future studies for this indication could conceivably utilize similar clinical trial design, with specific endpoints appropriately updated.

The rationale for use of oxygen carriers (systemically administered) in therapy of neoplasms is based on the observation that increased tumor tissue oxygen tension will increase the sensitivity of tumors to radiation or to chemotherapy more than that of normal tissue. Demonstration of increased oxygen tension in the target tumor can function as an important supporting argument for efficacy, but will not serve alone as the primary endpoint. Measurement of tumor responses and response rates, i.e., changes in tumor size, can be a valuable indicator of drug activity in phase II trials. Ultimately, the endpoint used to establish efficacy should be similar to that used in evaluation of cytotoxic agents for the stage and type of cancer under investigation.

B. Acute hemorrhagic shock

This category of indication involves a very complex clinical situation that is the subject of much investigation. The following specific points can be made:

1. Reversal of low blood pressure or cardiac output is important, but correction of these parameters alone is not a sufficient endpoint; such changes should be accompanied by other clinically meaningful events.

2. Field trials in severe trauma, where red blood cells are not routinely available, pose concerns related to safety and to ethical trial design. Available safety data have been obtained only under well defined clinical conditions and with small quantities of product and do not presently support the use of large volumes of oxygen carriers in recipients with multifactorial insults. In addition, there is some concern that such studies would be difficult to control and therefore complicate not only the trial design but also data analysis. Such studies, with existing oxygen carriers, are premature at this time. Trials in acute bleeding may be more feasible in the intensive care setting, however.

Investigators wishing to propose phase II studies in hemorrhagic shock should consider the comments provided. This is a complex clinical entity that is itself the subject of much investigation and it is appropriate to expect, and to accept, flexibility in the design of studies on hemorrhagic shock utilizing oxygen carriers.

C. Perioperative Applications

This category includes such situations as hemodilution (with or without autologous donation) and intraoperative replacement. Investigators should be aware of the present lack of objective criteria to define a broadly applicable transfusion trigger and should strive to develop and validate physiologic markers of efficacy for individual oxygen carriers.

It should be noted that decreased transfusion requirement has been accepted as the basis for efficacy of other alternatives to transfusion (erythropoietin). This endpoint could support the proposed efficacy of a red cell substitute if it were embodied within a suitable clinical trial design. It should be noted that, while decreased transfusion requirement may be regarded as a clinical benefit, trials of an oxygen carrier would need to evaluate potential disadvantages or risks to the patient receiving the oxygen carrier in lieu of transfusion, e.g., inferior perfusion, undesirable hemodynamic responses and other adverse drug reactions.

IV. CONCLUSIONS

1. Due to the fact that preclinical studies may not adequately predict potentially serious adverse reactions, understanding of safety in humans will be paramount.

2. FDA is prepared to review proposals for phase II trials of oxygen carriers for various indications, including their use as red cell substitutes. Investigators should understand that initiation of phase II (or phase III) trials for any product does not preclude the need to do additional phase I or preclinical studies if warranted by results. Such additional studies will be particularly important when unwanted, if not toxic, properties of an agent may affect efficacy.

3. Because of the limited understanding of red cell substitutes and their interaction with various disease states, proposed surrogate endpoints must be shown to meaningfully reflect clinical benefit.

4. FDA encourages investigators to develop and propose new markers of efficacy and will be as flexible as possible in evaluating these.